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(54)[Title of Invention] **Percutaneously Absorbable Levodopa-Containing
Preparation**

TECHNICAL FIELD

This invention relates to percutaneously absorbable levodopa-containing preparation

BACKGROUND OF THE INVENTION

Levodopa which is a dopamine precursor, exhibits biological activity by interior conversion in dopamine. Lately, a treatment of Parkinsonism, which causes dyskinesia, due to decrease of intra-cranial dopamine production, was carried out with levodopa circulating in the body and penetrating into the brain. That brought to symptoms improvement, due to conversion of levodopa to dopamine in nerve cells.

Levodopa is a widely used effective medicine as reported in Medicinal Journal; Vol. 31, No. 12, 1995/ p.2998

However, a daily treatment by levodopa administration is problematic.

- 1) Since levodopa easily generates metabolites with various tissues of digestive tract, only insignificant portion of levodopa penetrates into the brain, that requires the administration of the increasing dose.
- 2) Since half-life of levodopa in body is short, the persistency of drug efficacy is poor and in-day symptomatic changes are sharp.
- 3) An increase of the dose may cause a dyskinesia as a side effect.

On the other hand, this problem may be solved by manufacturing of enteric coating tablets for oral administration. Intravenous drip is also very useful to control dose and persistency.

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Moreover, metabolism of levodopa, which occurs before the levodopa transition into the brain, may be suppressed by the formulation containing an inhibitor of levodopa metabolism.

The proposed formulations were developed in order to increase the utilization coefficient of levodopa in the brain. However, concerning these types of administrations, it is difficult to restrict a sharp rise of levodopa concentration in the blood.

The increase of persistency is limited, since levodopa generates metabolites in digestive tract.

Furthermore, prolonged intravenous drip as a treatment of patients is complicated and causes pain.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a percutaneously absorbable levodopa-containing preparation, which increases the persistence of drug efficacy and applied externally.

The present invention comprises percutaneously absorbable levodopa-containing preparation (formulation) contained as a drug substance at least one component selected from among levodopa and pharmaceutically acceptable ester thereof in the base and the above mentioned drug exhibits its effect at a site other than the site of administration.

The formulation of the present invention preferably contains in the base an inhibitor of levodopa metabolism. In the present invention a desirable content of drug substance in the formulation is 0.1 ~ 30% w/w.

Concerning a particular situation in the present invention, the above described formulation in the base contains as an additive at least one compound selected from among organic acids, hygroscopic substances and surface active agents. As the hygroscopic substance it is preferable to use at least one compound selected from among water absorbing polymers and polyhydric alcohols.

Moreover, as a polyhydric alcohol it is preferable to use at least one compound selected among glycerin, propylene glycol, 1, 3 - butylene glycol and polyethylene glycol of molecular weight of 200 - 600 with final group.

Concerning the other aspects of the present invention, the base may be manufactured from at least one of the compounds selected from among polymers, silicic acid, silicates of

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earth metals, hydrocarbons, various oils, polyhydric alcohols, higher alcohols, lower alcohols, higher fatty acids, fatty acids esthers and water.

Further, the proposed formulation may be prepared at least in one of the following forms, selected from cream, gel, paste, lotion and cataplasm.

In the present invetnion, the percutaneously absorbable preparation is manufactured preferably by setting a layer of tackifier containing the active drug substance on one side of the support. Acrylic, rubber, silicon and urethan tackifier is preferable to use as a self-adhesive layer.

Moreover, acrylic tackifier preferably used is a copolymer prepared from 40 – 90 % mol. alkyl ester of (metha) acrylic acid with 10 – 60 % of vnyl pyrrolidone having a water absorption of more than 1.5%.

The active drug substance used in the present invention is at least one compound selected from among levodopa or pharmaceutically acceptable esthers thereof. It's content is preferably 0.1 – 30% w/w, since the increase of the drug content negatively affects the base properties and the decrease results in reduced efficacy.

In the present invention the inhibitor of metabolism may be used in order to suppress levodopa metabolism in the systemic circulation process and increase the transmittance through the skin. This provides an improvement of transition in the brain.

In addition this provides higher efficacy and , simultaiously, prevents a side effect of low blood pressure.

It is preferable to use as the metabolism inhibitor, for example benzazide HCl, carbidopa etc. It's desirable content in the base is 0.1-30% w/w.

In the present invention in order to increase percutaneously absorption of levodopa and esters thereof, the additives are added in the base, such as organic acids, hygroscopic substances and surface active agents.

Among them organic acids increase solubility of the drug substance in the base and in the skin. Hygroscopic substances increase transmittance through the skin and emission of the active drug substance from the base. Surface active agents decrease a barrier for drug substance and additives to pass through skin corneum.

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THE BEST WAY FOR EXPERIMENTAL EXERCISE OF THE PRESENT INVENTION

The following examples are intended to illustrate, but not to limit, the scope of the present invention.

Experimental Example 1

To levadopa (1.23 g) suspended in 19.87g glycerine, a 3.51g cross-povidone (1-vinyl-2-pyrrolidone cross-linked polymer) is added and the mixture is stirred to obtain a homogeneous paste.

Experimental Example 2

A mixture of 65% mol (302.0 g) 2-ethylhexyl acrylate (EHA), 35% mol (98.0 g) of vinylpyrrolidone (VP) and 0.02 weight part (80 mg) (relative to 100 weight parts of EHA and VP together) of hexamethyleneglycoldimetacrylate is transferred into a separating flask and 70.6 g of ethylacetate is added to provide a 85% w/w concentration of a starting monomer. The obtained mixture is heated to 65°C under an atmosphere of nitrogen. Ethylacetate and lauroyl peroxide, which is a polymerization initiator, are added in little portions and the reaction of polymerization is continued for 32 hours. Further, to 1.44 g of levadopa suspended in 2.49 g of glycerine and 2.49 g of cross-povidone (1-vinyl-2-pyrrolidone cross-linked polymer) is added to 62.75 g of the obtained polymer product in ethylacetate (solid matter content is 35.6%) and mixed to obtain a painting solution. Thus obtained painting solution is spread onto a 35 µm film of polyethyleneterephthalate (PET) treated with silicon, in order to achieve the levadopa content of 0.75 mg/cm² and the obtained preparation is dried at 60°C for 30 min to yield a tackifier layer. This tackifier layer is supported from the other side of PET film by laminating with ethylene-vinylacetate copolymer (EVA) to yield percutaneously absorbable patch with tacky layer.

Comparative Example 1

Sodium carboxycellulose (CMC-Na) (0.5 g) is dissolved in 100 ml water by stirring and 0.22 g of levadopa is added to 40 ml of this aqueous solution by stirring, to prepare the suspended formulation.

Evaluation of Performance

All formulations described in Experimental Example 1, 2 and in Comparative Example 1 are

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involved in this study, which is performed on rabbits by assaying of levadopa in rabbit blood.

(Determination of levedopa concentration in rabbit blood)

Levadopa is administrated as a percutaneously absorbable preparation, obtained as in Experimental Example 1,2. The tested preparations are applied on the shaved skin on the back of two different animals NZB (male, 1 year) on a skin surface of 200 cm² (3 g of the lotion prepared in Experimental Example 1 and the large patch of 200 cm² prepared in Experimental Example 2). The administrated dose is about 150 mg/animal.

On the other hand, the levadopa preparation from Comparative Example 1 is administrated orally (11 mg/kg or about 50 mg/animal) to third rabbit.

The blood is taken from these animals periodically during 24 hours and the concentration of levadopa in rabbit plasma is determined by HPLC. The obtained results are dmonstrated in Table 1.

Table 1

	Administration Way	Concentration of Levadopa in Rabbit Plasma (ng/ml)						
		0	0.5 hours	1.0 hour	2.0 hours	3.0 hours	6.0 hours	24 hours
Exp. Ex.1	Percutaneously	N.D	-	-	170	-	110	9.3
Exp. Ex.2	Percutaneously	N.D	-	-	26	-	27	13.5
Com.Ex.1	Orally	N.D	85	180	49	23	4.7	2.9

In Table 1 , N.D. – not detected.

(Experimental Examples 3 ~ 12, Comparative Example 2 and Literature Examples 1,2)

Tackifier A Preparation

A mixture of 25 g vinylpyrrolidone, 3 g of 2-ethylhexyl acrylate and 50 g of ethylacetate is transfered into a 5-necked flask, fitted with agitator, thermometer, reflux condensor, dropping funnel and nitrogen inlet pipe. In a nitrogen flow the mixture is stirred at 30 rpm and the temperature is elevated. Then, under a nitrogen flow the whole is refluxed for 30 min at the temperature lower than the boiling point. After discharge of the residual oxygen, the polymerization reaction in this mixture containing monomers is conducted at 70 °C. Ethylacetate is added to 1.0 g of lauroyl peroxide and the obtained solution (30 ml) is dropwise added (1 ml/h) to the mixture of monomers to conduct a copolymerization reaction. Within 3 hours after initiation of polimerization, 3 g of 2-ethylhexyl acrylate and 5 g of ethylacetate are added under a nitrogen bubbling and the copolimerization is

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continued. In addition, within 6 hours after initiation of polymerization 3 g of 2-ethylhexyl acrylate and 5 g of ethylacetate are added once more under a nitrogen bubbling and the copolymerization is continued. Within 35 hours after initiation of polymerization, the copolymerization is stopped, ethylacetate is added to obtain solution containing 30 % w/w of the solid matter and this solution is stirred, to obtain tackifier A in ethylacetate solution. The measured water absorption of the tackifier A is found to be 12.4 %.

Tackifier B Preparation

At the polymerization beginning, 25 g of vinylpyrrolidone, 75 g of 2-ethylhexyl acrylate and 120 g of ethylacetate are mixed to initiate a copolymerization. After initiation the same procedure, as in Tackifier A preparation is performed, but polymerization monomers are not added. Upon completion, ethylacetate is added to obtain solution containing 30 % w/w of the solid matter and this solution is stirred, to obtain tackifier B in ethylacetate solution. The measured water absorption of the tackifier B is found to be 1.0 %.

The compositions presented in Table 2, are the lotions (suspensions), prepared by mixing of the drug substance, tackifier solution, hygroscopic substance, any organic acid, surface active substance, additives and metabolism inhibitor to obtain a homogeneous preparation. These suspensions are spread onto polyethyleneterephthalate film and dried at 60°C for 30min to form a tackifier layer with thickness of 150 µm after drying. On thus obtained tackifier layer a laminate film consists of 12 µm of polyester and 20 µm of ethylene / vinylacetate copolymer is stucked to produce a patch.

Table 2

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|----------------------------------------|-------------------------------------------|
| 1) Levadopa amount | 7) Amount |
| 2) Patch | 8) Lactic acid amount |
| 3) Type | 9) Surface active substance* ² |
| 4) Amount | 10) Type |
| 5) Hygroscopic substance* ¹ | 11) Amount |
| 6) Type | 12) C.P.* ³ amount |
| | 13) Benzazide HCl amount |

Hygroscopic substance*¹ Gly : glycerin, PG: polyethyleneglycol.

Surface active substance*² BL9: polyoxyethylene (9) lauryl ether,
HE: sage oil polyoxyethylene(7) glycerin.

C.P.*³: Polyvinylpyrrolidone cross-linking agent.

Experimental Example 11

A mixture of 10 g of glycerine, 1 g of polyoxyethylenelauryl ether and 5 g of levadopa is mixed to obtain a homogeneous mixture A.

Then, a mixture of 15 g of glycerine, 5 g of sodium polyacrylate, 2 g of sodium carboxypropylcellulose and 0.3 g of aluminium glycinate is mixed to obtain a homogeneous mixture B.

In addition, 1g of gelatin is dissolved in 30 g of purified water at 60 °C to obtain a homogeneous mixture C.

Then, 0.2 g of tartaric, 3 g of lactic and 0.5 g of acrylic acids are added to 10 g of glycerin, mixed and the mixtures A,B and C are added. The resulting mixture is spread on polyester non-woven fabric (0.1 g /cm²) and thus treated fabric is laminated with polyester film yielding the percutaneously absorbable levodopa-containing preparation.

Percutaneous absorption evaluation

The study is performed on rats by periodical measuring (AUC) of levadopa concentration in rat blood up to 24 hours.

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Wistar rats (male, 7 weeks) with shaved skin on their backs are involved in this study. The 12 cm² samples of patches prepared as in Experimental Examples and Comparative Examples are stuck on the animal's skin.

On the other hand, 50 mg/kg (daily dose) of levodopa is administrated orally to other rats. The samples of rat blood are taken in 1, 2, 3, 6, 15 and 24 after each type of administration and levodopa concentration is determined in rat plasma by HPLC.

As presented in Table 3, since the AUC results in Experimental Examples are higher than 3000 ng • hr / L, in Comparative Examples are less than 600 ng • hr / L, it supposed, that percutaneous absorbtion in Experimental Examples is significantly high.

Further, the AUC result for oral administrated levedopa (2650 ng • hr / L) demonstrates, that in Experimental Examples all daily dose of levedopa is persistently absorbed.

Sample Stability

All patches prepared as above described in Experimental Examples and Literature Examples and packed in aluminium packing material are stored at 25°C for 1 month. Then, the plaster layer of each patch is checked to evaluate the presense of bleeding. The samples of Experimental Examples demonstrate, that their hygroscopic liquid component is stable, whilst each preparation from Literature Examples1.2 containing a significant amount of this component, having the tackifier B with lower water absorption, demonstrate bleeding. Thus, they are unstable.

Efficacy evaluation

The study for evaluation of percutaneously absorbable levodopa-containing preparation is performed on rats by inhibition of haloperidole provoked catalepsy.

Wistar rats (male, 7 weeks) with shaved skin on their backs are involved in this study. The 12 cm² samples of patches prepared as in Experimental Examples and Comparative Examples are stuck on the animal's skin. Within 1 and 20 hours after patch application haloperidole is orally administrated (1.0 mg/kg). After four hous, i.e. 5 and 24 after patch application, the levodopa efficacy is estimated by the method beneath descibed .

The efficacy is estimated as number of cases with observed catalepsy inhibition among 10 rats involved in the study.

Concerning the method for evaluation, a 2 mm Ø stainless steel pipe is set up above water surface (7 cm). Forefeets of the rat are attached to this pipe. The rat is removed from

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the pipe after the catalepsy retained position has been observed.

The period of catalepsy retention is more than 20 sec.

Table 3

- | | |
|-------------------------|-------------------------------------------------------|
| 1) Experimental Example | 4) Stability* ¹ |
| 2) Literature example | 5) Drug efficacy evaluation |
| 3) Comparative Example | 6) 5 hours * ² and 24 hours * ² |

*¹ 0: bleeding is not observed; X : bleeding is observed.

*²Time after the patch application

EFFECT OF THE PRESENT INVENTION

Sins, the present invention comprises percutaneously absorbable levodopa-containing preparation contained in the base as a drug substance at least one component selected from among levodopa and pharmaceutically acceptable ester thereof, administration of such preparation is very convenient, the effective concentration in the blood is persistently

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appropriate. Due to this property the side effect is reduced and sufficient drug efficacy is achieved with lower dose.

CLAIMS

- 1) Percutaneously absorbable levodopa-containing preparation containing in the base as a drug substance at least one compound selected from among levodopa and pharmaceutically accepted esthers thereof, the drug exhibits its effect at a site other than the site of administration.
- 2) Percutaneously absorbable levodopa-containing preparation, as claimed in item 1, contains inhibitor of levodopa metabolism.
- 3) Percutaneously absorbable levodopa-containing preparation, as claimed in item 1 and 2, contains 0.1 ~ 30% w/w of the active drug substance.
- 4) Percutaneously absorbable levodopa-containing preparation as claimed in each of items 1 – 3, contains as the additive in the base at least one compound selected from among organic acids, surface active agent and hygroscopic agent.
- 5) Percutaneously absorbable levodopa-containing preparation, as claimed in item 4, contains a hydroscopic substance, which is at least one compound selected from among water absorbing polymers and polyhydric alcohols.
- 6) Percutaneously absorbable levodopa-containing preparation, as claimed in item 5, contains a polyhidric alcohol, which is at least one compound selected among glycerin, propylene glycol, 1, 3 – butylene glycol and polypropylen glycol of molecular weight of 200 ~ 600 .
- 7) Percutaneously absorbable levodopa-containing preparation, as claimed in each of the items 1 – 6, contains the base, which is at least one of the compounds selected from among polymer, silicic acid, silicates of earth metals, hydrocarborns, various oils, polyhydric alcohols, higher alcohols, lower alcohols, higher fatty acids, fatty acid esthers and water.
- 8) Percutaneously absorbable levodopa-containing preparation, as claimed in each of the items 1 – 7, prepared in the form, which is at least one of the members selected from cream, gel, paste, lotion and cataplasm.
- 9) Percutaneously absorbable levodopa-containing preparation, as claimed in each of the items 1 –6, is a patch with tacky layer contained the active drug substance and

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located on one side of the support.

- 10) Percutaneously absorbable levodopa-containing preparation, as claimed in item 9, produced with the tackifier layer, which is at least one of the substances selected from among acryl tackifier, rubber tackifier, silicon tackifier and urethan tackifier.
- 11) Percutaneously absorbable levodopa-containing preparation, as claimed in item 10, produced by acrylic tackifier, which is a copolymer with water absorption of more than 1.5% and consisting of 40 – 90 % mol. of alkyl-(metha) acryl ester and 10-60% mol. of vinylpyrrolidone.